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MS/05/12544

GOVERNMENT OF INDIA
PATENT OFFICE
Ministry of Commerce and Industry
Department of Industrial Policy and Promotion

It is hereby certified that annexed here to is a true copy of **Application, Provisional Specification & Abstract** of the patent application as filed and detailed below:-

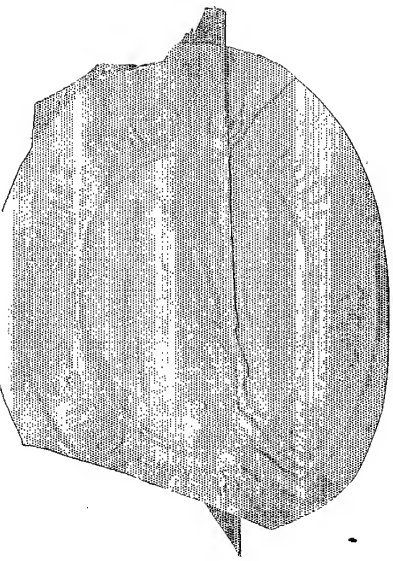
Date of application : **15-04-2004**

Application No : **346/CHE/2004**

Applicants : **M/s. Dr. Reddy's Laboratories, Generics an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, A.P., India.**

In witness there of
I have here unto set my hand

Dated this the 19th day of May 2005
29th day of Vaisakha, 1927(Saka)



By Authority of
THE CONTROLLER GENERAL OF PATENTS, DESIGNS AND TRADE MARKS.

M. S. V

(M.S.VENKATARAMAN)
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Received Rs 3000/- in Cash
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Vide C.B.R. No. 7902.

15/4

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7 and Rule 33A)

We, Dr. Reddys Laboratory Generic SBU, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "***A Stable Multiple Unit Dosage Form Comprising Amorphous Drug Substance.***"
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are Pavak Kumar Rajnikant Mehta, Akhilesh Ashok Dixit, Kiran Krishnan, Indu Bhushan, and Mailatur Sivaraman Mohan.
   All citizens & residents of India belonging to Dr. Reddy's Laboratories Generics SBU, 7-1-27, AMEERPET, HYDERABAD - 500 016
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows ;
   The General Manager,
   Research & Development,
   Dr. Reddy's Laboratories Ltd., Post Box No.15,
   Kukatpally, Hyderabad- 500 072, (A.P.) India
5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed)_____
PAVAK KUMAR RAJNIKANT MEHTA

(Signed)_____
AKHILESH DIXIT

(Signed)_____
KIRAN KRISHNAN

(Signed)_____
INDU BHUSHAN

(Signed)_____
M.S.MOHAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
   (a) provisional specification (09 pages, in triplicate, with Form 2)
   (b) abstract of the invention (01 page, in triplicate)
   (c) fee Rs. 3000.00 (three thousand rupees only) in bank draft bearing no 789469 dated 30.12.2003 drawn on HDFC bank.

We request that a patent may be granted to us for the said invention

Dated this Fourteenth day of APRIL-2004

(Signed)_____
M.S.Mohan
General manager – R & D
Dr. Reddy's Laboratories, Generics

The Controller of Patents and Designs
Patent Office Branch, Chennai- 600 090.

FORM 2

THE PATENTS ACT 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

A STABLE MULTIPLEUNIT DOSAGE FORM COMPRISING AMORPHOUS DRUG SUBSTANCE

Dr. Reddy's Laboratories, Generics

an Indian Company having its registered office at

7-1-27, Ameerpet
Hyderabad - 500 016, A.P., India

The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

A STABLE MULTIPLEUNIT DOSAGE FORM COMPRISING AMORPHOUS DRUG SUBSTANCE

Field of Invention

The present invention relates to multiple unit pharmaceutical dosage form for oral use, containing an amorphous drug substance and to a method of manufacturing of such preparations.

Background of Invention

Amorphous materials have properties that can be of advantage in the preparation of solid dosage forms, such as solubility, bioavailability, functional mechanics and adhesivity. However, the increased reactivity of an amorphous solid, with a consequent high propensity to spontaneous transform to the crystalline state at a certain relative humidity, force and temperature, may negatively affect the physical and chemical stability of the pharmaceutical preparation. The use of drugs and excipients in amorphous form represents both a potential advantage and disadvantage to the formulator. Attempts, have therefore, been made to overcome the disadvantages by modulating the solid-state reactivity of amorphous substances, in terms of increasing or decreasing their reactivity. The various approaches used for the formulation of an amorphous material involves the use of dry granulation technique for tabletting, complexation, dry mixing. melt extrusion, co-precipitation, spray drying and co-milling.

But there has always been need to produce a dosage form wherein the drug to be in the amorphous form either during the formulation process, or during the shelf life of the tablet or capsule.

Retaining the drug in the amorphous form in the final dosage form improves the dissolution of the final dosage form. The literature cites that dissolution rates increase in the following order: pure drug substance < physical mixture < solid dispersion < melt granules < amorphous drug < tableted melt granules.

Description of the prior art:

The various methods of making amorphous product include: spray drying, freeze drying (lyophilisation), melt precipitation, vapour condensation, crash cooling, from supercritical fluids e.g. using Solution Enhanced Dispersion by Supercritical fluids (SEDS), Rapid Expansion of Supercritical Solution (RESS) processes etc., co-precipitation with suitable excipients (these include sugars, acids, polymers, insoluble or enteric polymers, surfactants) to form solid dispersions, molecular dispersions, co-precipitates or co-evaporates by melting or fusion, or from solvents, including supercritical solvents.

It is well known that amorphous materials posses improved compression characteristics over the crystalline form. For example, commercial grades of lactose are produced by a spray drying technique to introduce some amorphous content which improves the compression force/hardness profile of the excipient (Handbook of Pharmaceutical Excipients, 3rd Edition, A. H. Kibbe, Pharmaceutical Press, p. 276).

Amorphous materials do not exhibit the three-dimensional long-range order found in crystalline materials but are structurally more similar to liquids where the arrangement of molecules is random. Amorphous solids are not crystalline and therefore do not give a definitive x-ray diffraction pattern, in addition they (to not give rise to a melting point and tend to liquify at some point beyond the glass transition point (Hancock and Zografi, (1997) J. Pharm. Sci., 86:1-12).

While the amorphous form of the drug has distinct physicochemical properties but it has a persistent problem in terms of maintaining the amorphous form of the drug on storage. Often the crystalline form of the drug has a lower free energy, and thus over time, the amorphous drug will tend to crystallize. The rate of crystallization may be influenced by storage conditions, such as temperature and humidity, as well as the constituents of the composition.

In the manufacture of drug substances or in the processing of pharmaceutical solids degrees of disorder through the formation of defects and amorphous regions are often observed. The amorphous state is mostly detected after lyophilization, spray drying or milling. It results in an higher energy state than the crystalline state. This can result in more advantageous properties such as enhanced dissolution rate or better tabletting properties. Often it is associated with increased chemical instability and difficulties in mixing and milling. Solid-state transformation upon storage is the most common and undesirable property since the driving force is the kinetic, which is often difficult to maintain as slow as possible. Furthermore depending of the conditions metastable or stable forms may result. Amorphous forms are hygroscopic and absorbed water plays the role of plasticizer, resulting to the lowering of the glass transition. It results an accelerated process of crystallization. The form of the crystal is highly unpredictable. The change of the form of the drug substance effects the quality of the drug product. The quality of the drug product is affected in terms of the change in the purity, identity and bioavailability of the drug product.
Several attempts have been made in the past to overcome these problems

Babcock, Walter C. ; et al. in the Patent application no **20030104063 teach that** A pharmaceutical composition comprises a dispersion comprising a low-solubility drug and a matrix combined with a concentration-enhancing polymer. At least a major portion of the drug is amorphous in the dispersion. The

compositions improve the stability of the drug in the dispersion, and/or the concentration of drug in a use environment.

Batycky, Richard P. ; et al. have discovered an improved way to achieve dissolution of poorly soluble drugs without sacrificing targeted flowability, wettability, selective agglomeration or annealing, yield or polymorphic stability. The invention is drawn to particles for oral drug delivery produced by ***spray-drying*** a dilute solution of a poorly soluble agent. The particles comprise regions of poorly soluble agent wherein the dissolution rate enhancement is between about 2-fold and about 25-fold compared to the agent in bulk form. Accordingly, what is still desired is a composition comprising an amorphous drug that is physically and/or chemically stable under typical storage conditions, may be formed via practical processing conditions, and that may enhance the bioavailability of poorly soluble drugs. These needs and others that will become apparent to one of ordinary skill are met by the present invention, which is summarized and described in detail below.

Objective of Invention:

Objective of present invention is to develop a pharmaceutical composition comprising amorphous form of the drug.

Another objective of the said invention is to process the amorphous form of a drug such that the amorphous form is retained in the final dosage form during processing or stability.

Another objective of the said invention is to develop multiple unit dosage form containing an amorphous drug.

Description of Invention:

The prior art references have cited that there is a conversion of the amorphous form to crystalline form by the conventional tabletting procedure and in presence of moisture. The inventors in their attempt to formulate several amorphous drug substances have discovered that the amorphous drug substance on subjecting to wet granulation, drug layering through coating or compression in conventional tablet compression machine has shown changes in the form from amorphous to crystalline. The presence crystalline drug in the final dosage effects the dissolution when compared to the dosage form containing the pure amorphous form of the drug in the final dosage form.

But to their surprise the inventors have found that the tablets produced by the use of a lower compression force did not render any change in the amorphous form of the drug.

The production of the minitablets of the amorphous drugs by using a dry process has shown that there is no conversion of the amorphous form

The Minitablets constitute the multiple-unit dosage forms are not only inexpensive, but also save time and flexibility in designing the dosage forms. They can be realised by filling small particles, usually pellets, into capsules. Minitablets, which are in this work tablets with a diameter smaller than 3 mm, are an interesting alternative in producing multiple-unit dosage forms. They are made by ordinary tabletting machines by direct compression, using a multiple tooling. There are several advantages for the use of minitablets because of their production process and due to their product properties.

The reference in the literature shows that minitablets show a lower resistance against densification and can be compressed to graded relative densities at lower pressures. This increased densification under pressure leads to both higher permanent densification and higher elastic densification, which in turn results in higher elastic recovery. The scientists discovered that by using a multi tip

tooling at a compression force of 0.5-3 ton for the tablet of 1mm to 3mm diameter they were able to avoid the conversion of the amorphous form. Further investigations revealed that the compression force applied to the punch gets distributed among the multiple punch tips there by leading to the reduced compression force on the tips.

It was also observed that the mini tablets also have reduced capping tendency when compared to the conventional tablets.

The minitablets have moreover shown to have several advantages over the conventional tablets. The advantage of minitablets lies in their precision of size. This guarantees a high degree of dosage precision. Each individual minitablet meets all the requirements of a single-dose drug form, such as uniformity of mass and content. They can therefore also be used individually as "solid drop".

The comparative invitro evaluation of the final dosage form containing the crystalline and amorphous form of the drug has revealed that the amorphous form of the drug shows superior dissolution characteristics when compared to the crystalline form of the drug with respect to the reference. The same is shown in figure 1.

The invention can also be applied to crystalline form of the drug, which is sucesptible to polymorphic conversion to different crystalline form.

The invention can be applied to all the amorphous drugs that are susceptible to conversion of crystalline form during processing or during storage. The examples of the drugs formulated using the approach are as below.

Conclusion

The multiple unit dosage form containing minitablets is a novel approach to formulate an amorphous drug, to maintain the amorphous form during processing and in the finished dosage form. Thereby the quality of the product

is not effected during processing or storage. The drug administered has shown to have higher bioavailability compared to the crystalline form.

List of figures

Example 1

Sr No.	Ingredients	40 mg Quantity (mg)	20 mg Quantity (mg)
Core		44.5	22.30
1	Esomeprazole Magnesium	242	264.20
2	Pearlitol SD 200	17.5	17.5
3	L HPC (LH-11)	20	20
4	Magnesium Oxide	7	7
5	Sodium Lauryl Sulphate	3.5	3.5
6	Colloidal Silicon dioxide	17.5	17.5
7	Sodium stearyl fumarate		
Core Weight :		**352**	**352.00**
Sub Coat (Considering maximum 4 %)			
	Zein F 6000	12.00	12.00
	Eudragit L 100 ;55	1.90	1.90
	Triethyl citrate	0.19	0.19
	Water	q.s.	q.s.
	Isopropyl alcohol	q.s.	q.s.
Subcoat weight		**366.09**	**366.09**
Enteric Coat (Considering maximum 25%)			
	Eudragit L100:55	80.27	80.27
	Triethyl citrate	8.06	8.06
	Glyceryl monostearate	1.6	1.6
	Titanium dioxide	1.6	1.6
	Isopropyl alcohol	q.s.	q.s.
Enteric coated weight		**457.62**	**457.62**

Manufacturing process Esomeprazole Mg Delayed release pellets:

1.Minitablets were manufactured by mixing excipient 1 to 7 and the dry mixture was directly compressed into minitablets.

Minitablet
Diameter 2.5mm
Thickness 1.6 to 1.9 mm
Avg weight 11 mg

2. Above minitablets were further subcoated with solution of zein and Eudragit L-100 – 55 in isopropyl alcohol and water

3. The subcoated minitablets were then enteric-coated using solution consisting Eudragit L-100 – 55. Glyceryl monostearate and triethyl citrate in isopropyl alcohol.

4.Finally enteric coated minitablets were filled into hard gelatin capsules. Around 44 to 46 minitablets were filled into each capsule

Abstract

The invention deals with the prevention of conversion of amorphous form of the drug to the crystalline form by using multiple unit dosage form technology for the formulation of a amorphous drug.